Physiology of Bile and Bilirubin

Introduction

This lesson focuses on the physiology and pathology of bile and bilirubin. Bile is produced by the hepatocytes, stored in the gallbladder, and released into the duodenum in response to a meal. There are numerous substances within bile. The three we care about are bile salts, bilirubin, and water. Water means that bile is an aqueous environment. Bile salts are amphipathic, having both a polar hydrophilic region and a nonpolar, lipophilic region. Bile salts are conjugated by hepatocytes, making them more water soluble, which results in their staying in the lumen of the intestine longer. Bile salts are the digestive component of bile, synthesized by the hepatocytes, stored in the gallbladder, released into the duodenum in response to a meal to digest ingested lipids. Bilirubin is a waste product of red blood cell turnover, a product of hemoglobin degradation. Bilirubin is conjugated in hepatocytes, making them more water soluble, which results in it staying in the lumen of the intestine, favoring its elimination in the stool. The link between bile salts and bilirubin may not seem obvious at first, but their biochemical similarities result in similar physiology. Both bile salts and bilirubin can be deconjugated and protonated in the intestines (both small intestine and large intestine), creating a lipophilic molecule that is passively absorbed by the intestines. Bile salts are meant to digest lipid and are also actively reabsorbed in the terminal ileum. Bilirubin is a waste product that is meant to be eliminated but is reabsorbed passively, given the similarities to bile salts, has no active transport, but is deconjugated by bacteria in the colon. The desired enterohepatic recirculation of bile salts (conserving the lipid-digesting enzymes for reuse) results in the undesired reabsorption of bilirubin. This lesson will explore the process of enterohepatic recirculation and bilirubin metabolism, then how to evaluate a patient who has elevated bilirubin levels and close with the exploration of some of the congenital causes of jaundice.

We will review the histology and anatomy of the biliary tree and gallbladder, then how the duodenum summons bile. This will close the loop that began with the physiology of gastric secretion and the digestion of lipids from Absorption: Start To Finish. You'll use this information to tackle the pathophysiology of hepatic jaundice in this lesson, and then to take on obstructive jaundice—autoimmune cholangiopathies, gallstones, and malignancies—in the next.

Bile Begins in Hepatocytes and is Conducted by Cholangiocytes

Hepatocytes are connected to each other by desmosomes and tight junctions immediately adjacent to their apical (canalicular) surfaces. Between those tight junctions lies the **bile canaliculus**, the earliest formation of a bile duct. The hepatocyte secretes bilirubin, bile acids, cholesterol, and phospholipids through the apical (canalicular) membrane. As the bile canaliculi approach the portal canal, still within the lobule, they form the canals of Hering. The canals of Hering are lined with both cholangiocytes of ductules and hepatocytes of lobules. These canals of Hering are the source of the hepatic stem cells. We will see these canals again in Hepatobiliary #5: *Cirrhosis*. The canaliculi (lined with hepatocytes) merge to form **ductules** (lined with cholangiocytes). Ductules progressively enlarge to become ducts. **Intrahepatic ductules** carry bile to **extrahepatic ducts**.

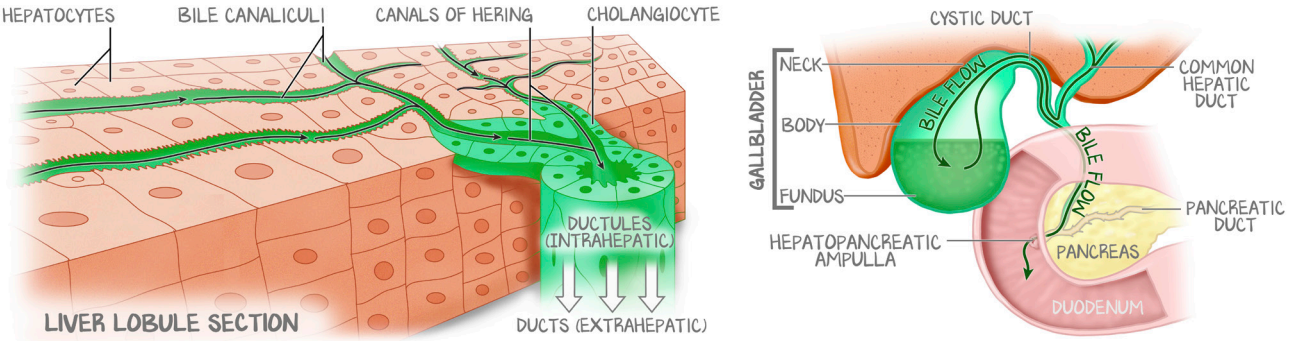

Figure 2.1: Bile Begins in Hepatocytes
Hepatocytes (the peach things) are much larger than the cells that line the intrahepatic ductule (the canal lined with many green cells). Bile is made by hepatocytes, secreted into the canaliculi between hepatocytes, and flows to the canals of Herring, the beginning of the ductules. Eventually, intrahepatic ductules become extrahepatic ducts. The left and right hepatic ducts converge into the common bile duct. The cystic duct branches from the common bile duct into the gallbladder. When the gallbladder contracts, the bile goes into the common bile duct, where it meets the pancreatic duct at the hepatopancreatic ampulla (ampulla of Vater).

The extrahepatic ducts make up the biliary tree. The biliary tree starts with the **left hepatic duct** coming from the left hepatic lobe and the **right hepatic duct** coming from the right hepatic lobe. The left and right hepatic ducts form the one **common hepatic duct**. The gallbladder is tucked under the liver. The gallbladder's **cystic duct** connects it to the common hepatic duct, thus becoming the **common bile duct** distal to the cystic duct. The common bile duct connects with the pancreatic duct very distally, almost near the opening to the duodenum. The stretch of the duct that is the final conduit to the duodenum is called the **hepatopancreatic ampulla** (ampulla of Vater). The hepatopancreatic sphincter (sphincter of Oddi) separates the ampulla from the duodenum at the greater papilla, the papilla of Vater.

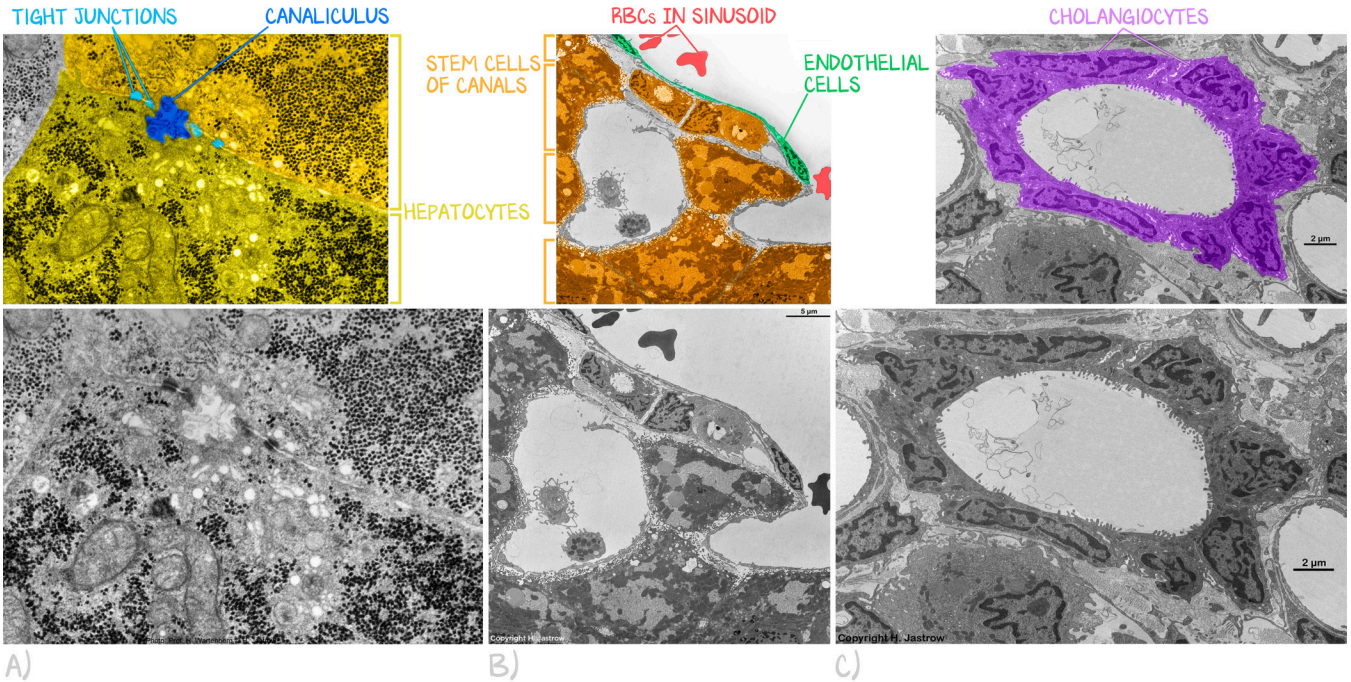

Figure 2.2: Electron Microscopy of Ducts and Cholangiocytes
(a) A single bile canaliculus between two hepatocytes can be seen in the top center of the image. The hepatic microvilli litter the shared space. From the canaliculus is a dark grey band in the intercellular space, a patch of white, and then an even darker grey band. The first lighter grey is the zona adherens that seals the canaliculus. The darker band is the zona adherens, the desmosomes that keep the hepatocytes together. (b) Canals of Hering. Present are the stem cells that could become bile duct cells, hepatocytes, and endothelial cells lining a large-lumen vessel (in which are red blood cells). (c) A large intrahepatic ductule, lined with ten cholangiocytes.

The cells of the ducts and gallbladder are called **cholangiocytes**. They are columnar and have microvilli on their apical surface. As the ducts get larger, they acquire a large elastic layer. The epithelium stays simple columnar. Cholangiocytes of the biliary ducts are similar to the cholangiocytes of the pancreatic ducts in that they secrete bicarbonate and chloride, line ducts, and respond to secretin. Although all simple columnar epithelium, the function of cholangiocytes changes based on their location in the ductal system, mediated by the proteins in the apical domain. Cholangiocytes line ducts that bring bile to the gallbladder and from the gallbladder to the duodenum.

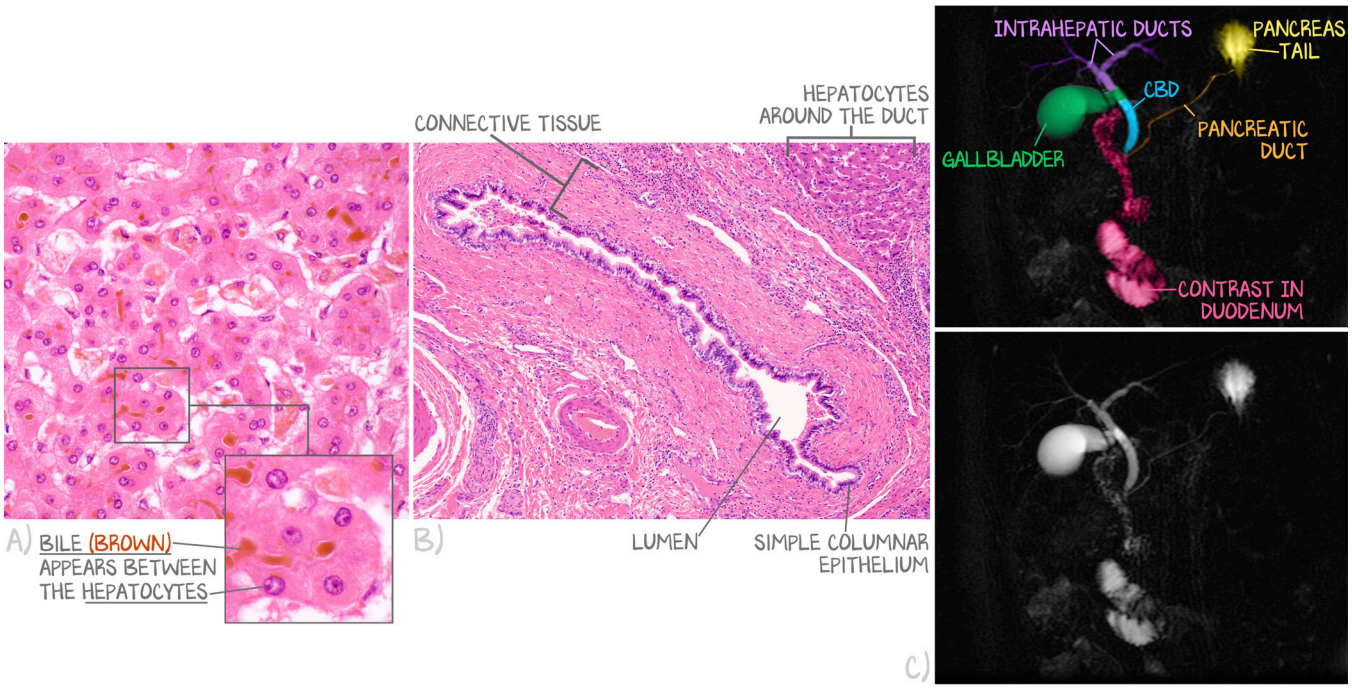

Figure 2.3: Light Microscopy of Ducts and Cholangiocytes
(a)The bile canaliculi are the smallest structures where bile begins its journey from hepatocytes. A bile canaliculus is an intercellular space (about 1 micron in diameter) that is formed by the apposition of adjacent surfaces of two or three hepatocytes. These surfaces have cut-out areas so that when they come together, they form a circular bile canaliculus. Bile is brown on this H&E stain and denotes the location of canaliculi. (b) This intermediate magnification view of liver shows a large intrahepatic bile duct. It is lined by simple columnar epithelium and contains elastic tissue within its walls. (c) A normal MRCP labeled to demonstrate the gallbladder, the biliary tree, and the pancreatic duct, which connect to the common bile duct near the duodenum.

The Gallbladder

The gallbladder houses and concentrates bile. Bile is made by hepatocytes and is secreted into the canaliculi. The bile is drained into the gallbladder, which, relaxed at rest, stores that bile. The gallbladder is formed from the same bud of the foregut that makes the pancreas and liver. It is derived from the endoderm. Its vascular supply originates from the celiac trunk, just like the liver and the pancreas. Its purpose is simple—store bile, absorb water from bile, contract when instructed to. That contraction forces bile down into the duodenum. The signal that calls for bile is the same signal that calls for pancreatic secretion—secretin (duct cells secrete bicarbonate-rich fluid) and CCK (gallbladder contraction) from the duodenum.

The gallbladder needs to contract in order to expel the bile when signaled to do so by the duodenum. The mucosa is a simple columnar epithelium that forms its own equivalent of villi—evaginations of lamina propria lined with columnar epithelium off the muscularis externa. Yep. You did read that

correctly, and we didn't have a brain fart. The gallbladder **lacks a muscularis mucosae** and **lacks a submucosa.** Even though it is made from the foregut, the gallbladder's mucosa lacks a submucosa and muscularis mucosae. That doesn't mean anything special; it's just striking at first (and learners often confuse muscularis mucosae with muscularis externa when first learning the layers of the GI tract). The muscularis externa has seemingly randomly oriented smooth muscle and numerous bundles of collagen and elastic fibers. This arrangement allows the gallbladder to contract in all planes, pushing stored bile through the cystic duct and into the common bile duct. There is no peristalsis in the gallbladder; it just gets smaller, so it squeezes bile out slowly, as if squeezing a tube of toothpaste from the bottom up.

The cholangiocytes of the gallbladder **absorb water from the bile**. They actively pump sodium and chloride into the intercellular space. Water follows salt passively through aquaporins. The hydrostatic pressure pushes the fluid into the vessels under the basement membrane of the lamina propria. Prolonged periods without emptying the gallbladder can lead to sludging and gallstone formation, as the water that the gallbladder absorbs keeps biliary fluid dilute enough to prevent precipitation.

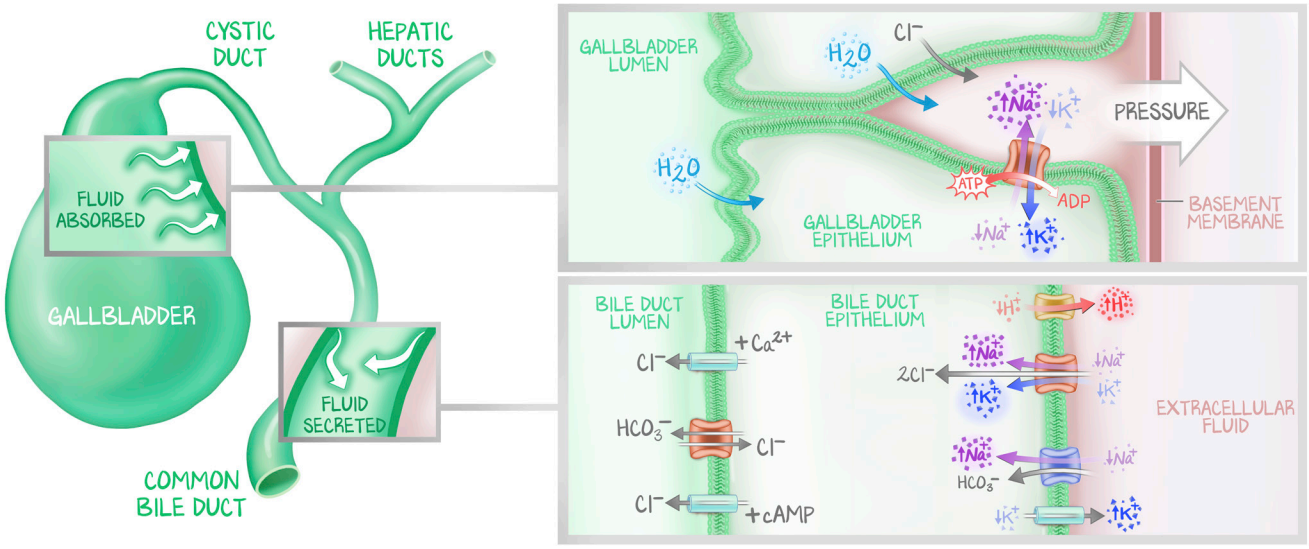

Figure 2.4: Cholangiocytes
Cholangiocytes of the gallbladder absorb water and concentrate bile. Cholangiocytes of the bile duct secrete bicarbonate and fluid. Those pumps look scary now because you aren't expected to have done Renal. We aren't emphasizing them, other than to show you "bicarb traded for chloride" in the ducts (like in the pancreas), and water follows salt (like everywhere).

The vascular supply comes from a branch of the celiac trunk, carried in the hepatoduodenal ligament. The **cystic artery** is a branch of the proper hepatic artery.

Flow Through the Biliary Tree

Hepatocytes secrete osmotically active compounds into the bile canaliculi. Water follows to balance the osmotic load. This results in an isotonic solution; water moves to balance the concentration gradient established by the secretion of those osmotically active compounds. Flow rates can increase by increased bile acid production (osmotic flow increases), contraction of the gallbladder (mechanical push), or the production of the aqueous component of bile by cholangiocytes.

Recall that in the duodenum, in response to acidic contents and the presence of fats and proteins, S cells release **secretin,** and I cells release **cholecystokinin** (CCK, Chole- Cysto- Kinin). These were just two of the enterogastrones. These were the two that induced the acinar cells of the pancreas to secrete zymogens (CCK) and the ductal cells to secrete a bicarbonate-rich fluid (secretin). Here they are, back again.

Flow changes with gallbladder contraction. A contracting gallbladder is a mechanical force that squeezes the biliary system, forcing flow to the duodenum. Gallbladder contraction is stimulated by the enterogastrone CCK and vagal stimulation via ACh. Just like in the pancreas, we want you to think, "organ CCK, ducts secretin." So, although it is true that everything influences everything else, learn that CCK and ACh lead to gallbladder contraction.

Flow also changes through the stimulation of the cholangiocytes of the biliary ducts. They secrete an aqueous solution rich in bicarbonate. Secretin also induces pancreatic ductal cells to secrete a bicarbonate-rich aqueous solution and uses the same channels as the cholangiocytes. The same signal activates the same channels through the same mechanism, resulting in the same outcome—more flow, more water, more bicarb.

The final way that flow changes is through the regulation of bile acid production and the enterohepatic recirculation, discussed next. The more bile acids that are made, the more the flow increases. More bile acids mean a greater osmotic load, and so more water diffuses into the canaliculi to balance osmotic forces.

Bile Salt and Bile Acid Metabolism

Bile salts are the polar, usually negatively charged, water-soluble version of their **bile acid** cousins. Bile acid is protonated (BA-H) and is thus nonpolar and lipid-soluble. Bile salts (BA–) can be further conjugated (BA-C–) but remain bile salts because they keep the negative charge. Hepatocytes both make bile acids from cholesterol and recycle bile acids returning from the gut (enterohepatic recirculation). Those that return as bile acids (neutral, lipophilic) are reabsorbed by passive diffusion through the lipid membrane. Those that return as bile salts require active transport (either a sodium cotransporter or bicarbonate antiporter). To reuse them, the bile salt form is pumped into the bile canaliculi via a bile salt-specific transporter (other organic ions, not bile salts, use a different transporter, as in bilirubin below). **Only the bile salt form** can access the aqueous bile. There, they are stored in bile within the gallbladder until released into the duodenum.

Bile salts allow for lipid digestion in the duodenum. They are amphipathic molecules with a hydrophilic region and a hydrophobic region. That means they are able to dissolve fat with the hydrophobic side and stabilize it in aqueous solution with the hydrophilic domain. That was the perspective of lipid digestion. Now we see things from the bile salts' perspective. Bile salts allow for lipid digestion. Bile acids get reabsorbed and so cannot participate in lipid digestion. The liver wants all the bile salts back but also needs the bile salts to stay in the intestine to get as much lipid digested and absorbed as possible.

Bile salts cannot be absorbed by the intestines because they are polar, and enterocytes lack transporters to absorb anionic molecules. Bile acids are absorbed by the intestinal enterocytes passively, without enterocyte transporters, because bile acids are protonated and, therefore, lipophilic and can pass through plasma membranes. The pH of the intestines is sufficient that some of the bile salts get protonated to bile acids and are reabsorbed along the way. But most of the bile salts remain bile salts and continue lipid digestion. At the end of the small intestine, in the **terminal ileum**, is where the liver gets most of the bile acids back. There is **active transport of bile salts** (and other organic acids) via **apical transporters** (some use sodium, some use bicarb). Those that are missed by the active transport are deconjugated by bacteria in the colon into bile acids, which are passively absorbed by the colon. A little passive reabsorption occurs along the intestine because the pH in the intestines protonates the bile salt to bile acid, a little passive reabsorption occurs in the colon because bacteria deconjugate the bile salt to bile acid, and **most of the reabsorption occurs by active transport in the terminal ileum**.

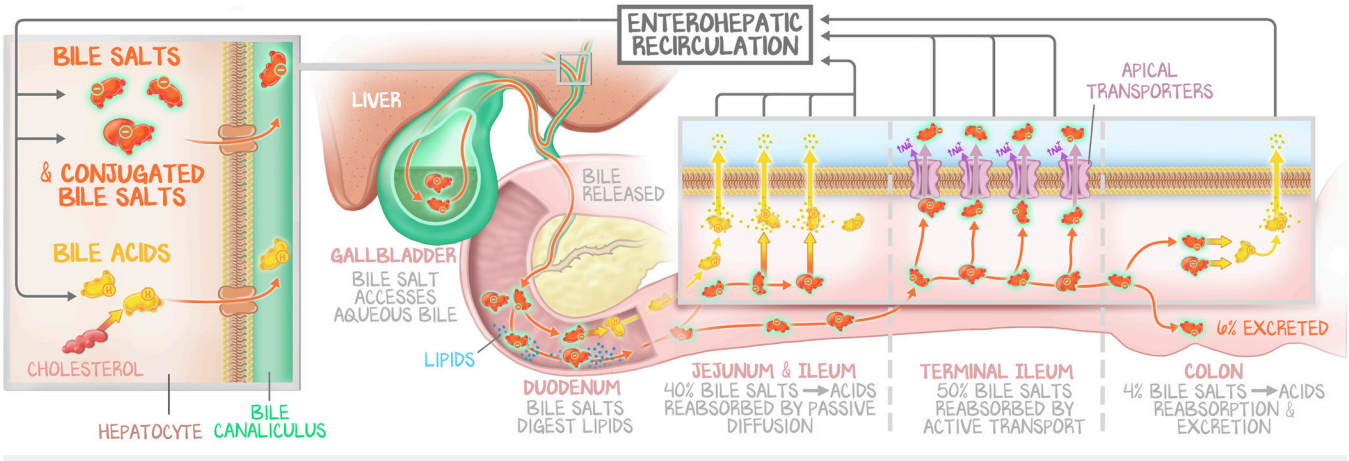

Figure 2.5: Enterohepatic Recirculation
Bilirubin and cholesterol are waste products in bile. Bile acids facilitate the digestion and absorption of fatty acids and cholesterol. Because the body reabsorbs bile acids while absorbing cholesterol and lipids, and because the waste products are lipophilic like the cholesterol and lipids, by reabsorbing bile acids (desired), the gut also reabsorbs bilirubin and cholesterol (not desired).

Hepatocytes then extract bile acids (passively, as they are lipophilic) and bile salts (actively, as they are hydrophilic) from the portal circulation. About 94% of bile salts/acids are recirculated this way in the **enterohepatic circulation**. The small amount lost to the stool is replaced by the liver, which uses cholesterol to synthesize more. The quantity of bile secreted by the liver is highly dependent on the availability of bile salts returning in enterohepatic circulation. The hepatocytes "know" how much they should be secreting and will keep up the production of new bile salts to match how much they "know" there should be. The **fewer bile salts that return** to the liver, **the more bile salts are synthesized**, and therefore the faster the rate of bile flow.

Bilirubin Metabolism

We now shift gears a bit and focus specifically on bilirubin metabolism. The story is identical to that of bile salts and acids, except, because bilirubin is a waste product of heme metabolism, there is no active transport in the terminal ileum. Bile salts were charged and therefore required active transport into hepatocytes from the blood, into enterocytes from the lumen, and could be turned into bile acids by bacteria. In the story of bilirubin, instead of "bile salt," we will say **conjugated bilirubin**. Bile acids were not charged and therefore required no active transport into hepatocytes or enterocytes, and so were reabsorbed by the intestines and the colon. In the story of bilirubin, instead of "bile acid," we will say **unconjugated bilirubin**.

A red blood cell has reached the end of its lifespan. Kupffer cells (resident macrophages) phagocytose the red blood cell and degrade it. Within that red blood cell is a lot of hemoglobin. The Kupffer cell degrades hemoglobin into globin (which then is broken down into its amino acids), iron (which the Kupffer cells store or release), and a heme ring. The heme ring is converted to biliverdin by heme oxygenase, then biliverdin is converted to unconjugated bilirubin by biliverdin reductase. All of this happens in the Kupffer cell lysosomes. Notice also that nothing was bolded. This will be explored in detail in Heme/Onc. This brings us to the start of our hepatocyte story.

Unconjugated bilirubin is released into the bloodstream by the Kupffer cell and is circulated attached to albumin. Unconjugated bilirubin is lipid-soluble (lipophilic) and not water-soluble (hydrophobic), and can pass through plasma membranes.

Unconjugated bilirubin follows three steps: uptake, conjugation, secretion. **Uptake** of unconjugated bilirubin from the blood into hepatocytes requires no transporter. In order to get the unconjugated bilirubin into the bile, it must be conjugated. **Conjugation** occurs via bilirubin uridine diphosphate glucuronosyltransferase. The enzyme is abbreviated UGT1A1 after the gene that codes for it, *UGT1A1*. Finally, **secretion** into the bile canaliculi occurs via active transport fueled by ATP via the apical (canalicular) transmembrane protein MRP2 (named multi-drug resistant protein 2, which doesn't help you know what it does, so learn MRP2). **Only conjugated bilirubin can access MRP2**, so only conjugated bilirubin can be excreted in bile.

From there, it is part of the bile. It is stored in the gallbladder and released with bile acids. Conjugated bilirubin is hydrophilic, that's what the conjugation did. There aren't bacteria in the duodenum or jejunum. No conjugated bilirubin is reabsorbed. A small fraction of conjugated bilirubin is protonated by the pH of the intestinal lumen, so a small amount of bilirubin is reabsorbed. There is no active transport in the terminal ileum. Almost all of the secreted bilirubin reaches the colon. The bacteria deconjugate all of it to unconjugated bilirubin. About half of the bilirubin is reabsorbed by the intestines (small and large together) as unconjugated bilirubin. The other half will be converted by colonic **bacterial proteases** into **urobilinogen**. 20% of urobilinogen is reabsorbed by the colon. The other 80% of urobilinogen is further metabolized by bacteria to **stercobilin** and is eliminated in the stool. Stercobilin gives stool its dark color. If bile cannot reach the GI tract, and the stool will be clay-colored.

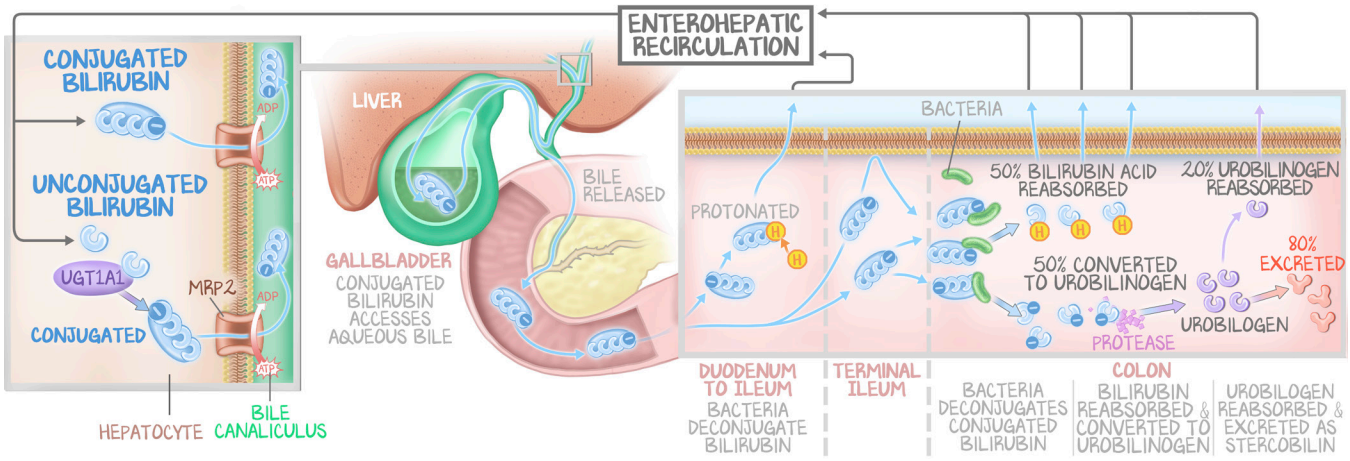

Figure 2.6: Enterohepatic Recirculation of Bilirubin
Amazingly similar to the enterohepatic recirculation of bile salts, with the exception that there is no active transport in the terminal ileum, and therefore most of the reabsorption occurs in the colon and much of the bilirubin is eliminated. Don't memorize these numbers, but this is the tally so far. 100% of bilirubin was secreted by hepatocytes. 50% was reabsorbed as unconjugated bilirubin, 10% reabsorbed as urobilinogen, and 40% eliminated in the stool. The point is that the mechanisms that facilitate bile salt recirculation (which the liver wants) also result in recirculation of bilirubin (which the liver does not want).

Of the urobilinogen that returns through the portal blood, almost all of it (80% of what returned, 8% of the original secreted) is turned back into unconjugated bilirubin and resecreted. The remaining (20% of what returned, 2% of the original) is **excreted by the kidneys**. Urobilin-ogen can pass freely through plasma membranes. In the urine, it is converted to urobilin, which is polar, trapping it in the aqueous urine to be eliminated. **Urobilin** gives urine its yellow color. The significance of this is that in order for there to be urobilinogen in the urine (which is normal), the bile must be delivered to colonic bacteria.

One of the things checked for on urinalysis is urobilinogen. **Urobilinogen in the urine is normal** and signifies that the bile secretion pathway is **open**. If bile cannot reach the GI tract, if there is an obstruction to biliary flow, urobilinogen will be negative in the urine.

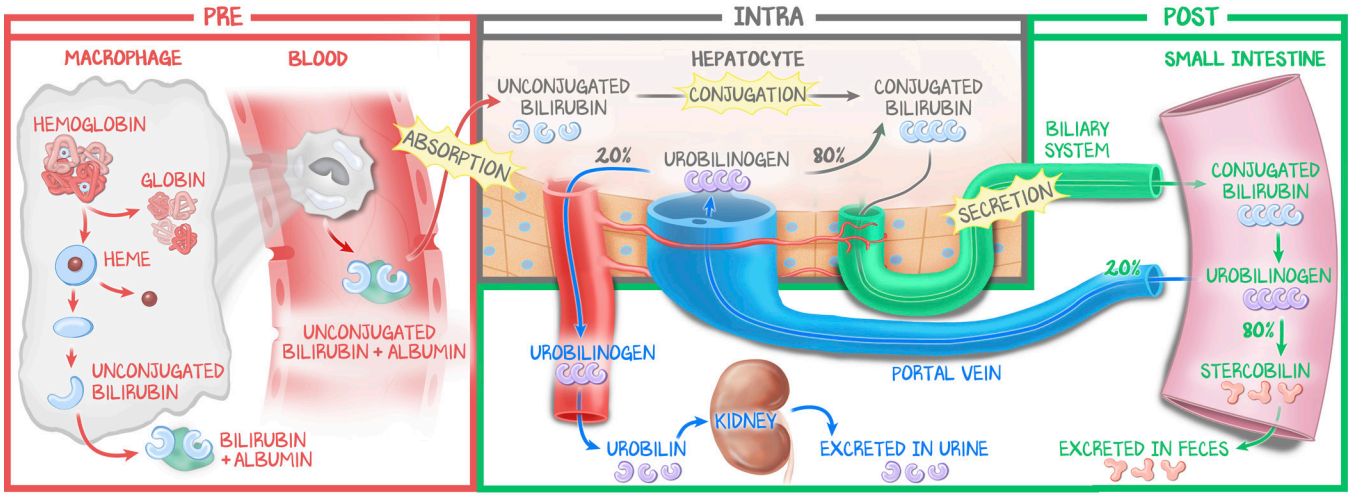

Figure 2.7: Bilirubin Metabolism
Kupffer cells destroy dead or dying red blood cells. The Kupffer cell converts heme to unconjugated bilirubin. Unconjugated bilirubin circulates on albumin in the blood. The unconjugated bilirubin is absorbed into the hepatocytes, conjugated by UGT1A1, and then released into the bile. Most (80%) of the conjugated bilirubin in the stool is converted to urobilinogen and then stercobilin, being excreted in the feces. 20% of urobilinogen is reabsorbed through enterohepatic recirculation. Of that, 80% is reconverted into conjugated bilirubin and sent back out through the bile. The 20% that remains is excreted in the urine as urobilin. Bilirubin is normally excreted in stool, but can also be excreted in the urine.

But we're not done yet. Because there is passive diffusion of unconjugated bilirubin, it can simply leave the hepatocyte and escape conjugation. That means **circulating unconjugated bilirubin is normal**. Too much of it is a sign of dysfunction. The liver maintains an equilibrium of low circulating bilirubin and bilirubin elimination.

Finally, if there is **circulating conjugated bilirubin** (of which there should be only a small fraction compared to the already small amount of unconjugated), it requires the use of an organic anion transporter protein (OATP), specifically OATP1B1 and OATP1B3, that uses ATP to bring bilirubin into the hepatocyte. Because it is already conjugated, it is pumped into the canaliculus by MRP2. Conjugated bilirubin is also freely filtered by the kidney, and, because it's already polar, is also trapped. The kidney has no means of handling unconjugated bilirubin, a feature that becomes useful in diagnosing hyperbilirubinemia.

Evaluation of Hyperbilirubinemia

When a patient has a disorder of bilirubin, bilirubin accumulates and deposits in all tissues. **Jaundice** (yellow skin) and **scleral icterus** (eyes) are visible symptoms of **bilirubin accumulation**. Unconjugated bilirubin is tightly bound to albumin, so it is not easily filterable by the kidney. When filtered, it is lipophilic and easily reabsorbed, passing through tubule cell membranes. In contrast, conjugated bilirubin is water-soluble and only loosely bound to albumin. Excess conjugated bilirubin is easily excreted in the urine. Accumulation of both unconjugated and conjugated bilirubin will lead to a **darkening of the urine**. The extent of urinary elimination is greater for conjugated bilirubin.

In the lab, bilirubin is assessed in the form of **total bilirubin** (both conjugated and unconjugated) and **direct bilirubin** (conjugated). The amount of unconjugated bilirubin must, therefore, be inferred or calculated.

Based on the metabolism of bilirubin, we can classify three stages of bilirubin disease: prehepatic, posthepatic, and intrahepatic. We introduce them here for context but discuss liver function tests specifically in Hepatobiliary #4: *Metabolic Liver Disease*.

Prehepatic is hemolysis. A preponderance of **unconjugated bilirubin** is suggestive of red blood cell turnover—hemolysis. Look for hemolytic anemia. Supportive evidence of hemolysis is **elevated LDH** and **low haptoglobin** levels. Haptoglobin binds to hemoglobin in plasma, so it will drop to undetectable levels when hemolysis is occurring. (See Heme/Onc for more on hemolysis.) Because the insult is prehepatic, the other liver function tests cannot be deranged. Hepatocytes remain unaffected, so only the bilirubin is elevated, and most of it is unconjugated.

Posthepatic is obstructive jaundice. A preponderance of **conjugated bilirubin** is suggestive of an obstructive process, after the hepatocytes. Uptake and conjugation are intact, but excretion—whether a defect of hepatocyte transporters, intrahepatic obstruction, or extrahepatic obstruction—is impaired. This is the subject of the next lesson. There are painless causes (cancer) and painful causes (gallstones). The degree and extent of the liver function test derangement will vary based on the cause. Acute obstructions of the biliary tree (gallstones) cause hepatocyte dysfunction and can elevate the AST and ALT. Chronic, insidious obstruction of the biliary tree (cancer) causes little hepatocyte dysfunction and can elevate the bilirubin into the double digits (normal < 0.5 mg/dL), while leaving the hepatocyte labs near normal.

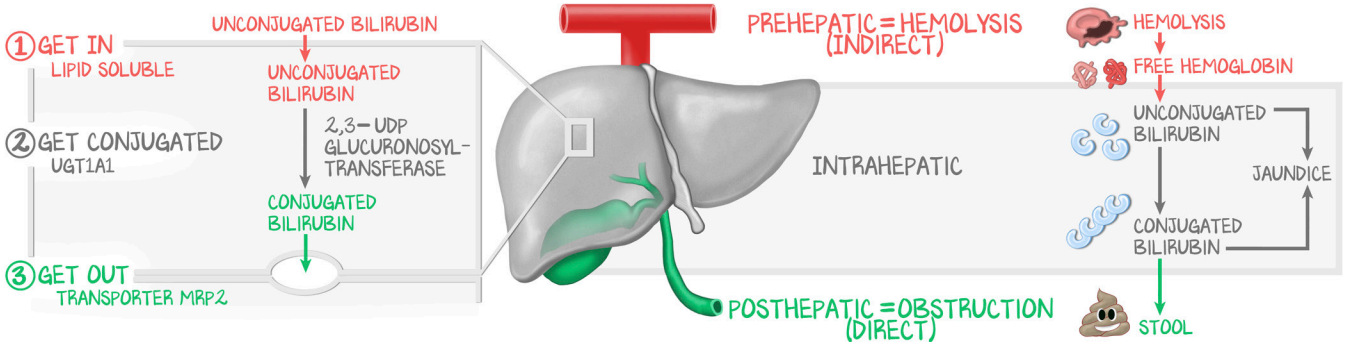

Figure 2.8: Approach to Hyperbilirubinemia
A simplified rendition of the causes of hyperbilirubinemia. Prehepatic jaundice is caused by hemolysis and will demonstrate mostly unconjugated hyperbilirubinemia. Posthepatic jaundice is caused by obstruction and will demonstrate primarily conjugated hyperbilirubinemia. Intrahepatic jaundice is more difficult to assess, as the presentation can be either conjugated or unconjugated hyperbilirubinemia. Suffice it to say, once pre- and post- have been ruled out, intrahepatic can be considered.

Intrahepatic is the one left over. In cirrhosis, the bilirubin can be elevated, and there is a relative split between conjugated and unconjugated. Some liver diseases (hereditary hyperbilirubinemias, below) can present either as prehepatic or posthepatic, yet the defect is in the hepatocyte. Fulminant hepatic failure will cause elevated bilirubin, and it cannot be predicted which type will be elevated.

The point of this teaching modality is essentially, *unconjugated hyperbilirubinemia is hemolysis, conjugated hyperbilirubinemia is obstruction, anything else is probably the liver.*

Neonatal Jaundice

Because the hepatic machinery for conjugating and excreting bilirubin does not fully mature until two weeks of age, almost every newborn develops transient mild unconjugated bilirubinemia. This is called **physiologic jaundice of the newborn**. There are two pathologic causes of neonatal jaundice related to breastfeeding: breastfeeding jaundice and breast milk jaundice.

Breastfeeding jaundice is an exacerbation of physiologic jaundice caused by impaired intestinal motility. If baby doesn't get enough food (whether it be mom's or from formula), then conjugated bilirubin has more time to be protonated and absorbed. This is fixed by feeding baby more. Bilirubin levels do not get high enough to cause problems for baby.

Breast milk jaundice is an exacerbation of physiologic jaundice believed to be caused by enzymes in mom's breast milk that impairs conjugation in baby's hepatocytes. It is not yet well elucidated. This is fixed by feeding baby formula for a while. Bilirubin levels do not get high enough to cause problems for baby.

The above baby jaundices occur in the first weeks of life and are not congenital. What follows, in the next section, is a discussion of hereditary jaundice. Most of the conditions do not cause jaundice at birth. Although congenital, they tend to provoke hyperbilirubinemia later in life and when stressed. Jaundice is such a big deal for babies because unconjugated bilirubin can deposit in the brain, called **kernicterus**, which results in mental retardation. The greater the bilirubin level, the more severe the retardation. Because it occurs so early in mental development, essentially any untreated pathologic levels will result in intellectual disability.

Hereditary Hyperbilirubinemia

These hereditary syndromes can be divided into those that cause unconjugated hyperbilirubinemia and those that cause conjugated hyperbilirubinemia. The first three cause unconjugated hyperbilirubinemia. There is a risk for kernicterus. The unconjugated hyperbilirubinemia syndromes are caused by alterations of the *UGT1A1* gene.

Gilbert (pronounced *Jeel-bear*) syndrome is caused by an **autosomal recessive** mutation of the *UGT1A1* gene that results in **decreased activity** of UGT1A1. There is no change to the hepatocytes on pathology, and the disease is completely innocuous. During times of stress, the patient will turn a little yellow. The levels do not get high enough to cause problems in childhood or adulthood. Although the hyperbilirubinemia caused by Gilbert syndrome is unconjugated, the mutation is so mild that it does not cause kernicterus. There is usually no jaundice in the neonatal period, even if stressed, as in premature deliveries. It is typically not seen, unidentified, and unknown in childhood, only to reveal itself in adulthood during a severe illness.

Crigler-Najjar type 2 is an **autosomal dominant** mutation of the *UGT1A1* gene that also results in **decreased activity** of UGT1A1. The degree of activity is similar to that in Gilbert syndrome, but slightly more impaired. Learn this disease to present just like Gilbert, except that if a neonate affected by Crigler-Najjar type 2 experiences a catastrophic insult (severe premature birth, twin-twin transfusion), kernicterus is *possible*. Crigler-Najjar type 2 does not present with neonatal jaundice if the neonate and gestation were healthy. If severe insult is incurred, such as premature delivery, respiratory distress of the newborn, or other severe stressors in the neonatal period, the neonate will become jaundiced. Later in life, just as in Gilbert syndrome, the patient will become minimally jaundiced when presented with a severe stressor.

Crigler-Najjar type 1 is an **autosomal recessive deletion** of *UGT1A1* and **absent** UGT1A1 activity. This is **fatal in the neonatal period**. It causes an accumulation of unconjugated bilirubin. The hepatocytes show no defect on histology. There is no treatment, and there is no cure. The kernicterus will be so bad that baby dies. This is fatal very quickly in the neonatal period, thus no child or adult will present with this syndrome.

The two that follow cause conjugated hyperbilirubinemia syndromes. The uptake and conjugation steps are not impaired. Thus, there is no risk of kernicterus. The disease course is innocuous. Like Gilbert, the patients get a little yellow when stressed.

Dubin-Johnson syndrome is caused by an **autosomal recessive** mutation of *MRP2* that leads to an **impaired biliary excretion**. The liver accumulates **pigmented cytoplasmic globules,** which gives it a **black appearance** on gross inspection—autopsy or during surgery. Nothing needs to be done for Dubin-Johnson. Like Gilbert and Crigler-Najjar Type 2, the only symptoms will be jaundice and mild hyperbilirubinemia during times of severe stress as an adult. Dubin-Johnson does not present during the neonatal period.

Rotor syndrome is also **autosomal recessive** and presents only with mild jaundice to stress, like Dubin-Johnson, but we are unclear as to the gene that is affected (medical science does know, we just don't want to disrupt the organizer). It is not *MRP2*. There are no pigmented cytoplasmic globules. So, Rotor syndrome does not present with a black liver. Like Dubin-Johnson, Rotor syndrome does not present in the neonatal period. Rotor syndrome is the other conjugated hyperbilirubinemia that does not present with a black liver.

Dubin-Johnson, conjugated, black liver; Rotor, conjugated, normal liver.

DIAGNOSIS	CLINICAL FEATURE	GENETICS	BILIRUBINEMIA	KERNICTERUS RISK
Gilbert	Unconjugated, not Crigler-Najjar	*UGT1A1*, AR	Unconjugated	None
Crigler-Najjar 2	Autosomal dominant	*UGT1A1*, AD	Unconjugated	Mild
Crigler-Najjar 1	Fatal	*UGT1A1*, AR	Unconjugated	Severe
Dubin-Johnson	Black liver	*MRP2*, AR	Conjugated	None
Rotor	Conjugated, not Dubin-Johnson	*uncertain* AR	Conjugated	None

Table 2.1: Genetic Hyperbilirubinemia
This table highlights the clinical feature that identifies the diagnosis, then links the diagnosis to genetics, bilirubinemia, and clinical significance.

Citations

Figure 2.2: © H. Jastrow www.drjastrow.de licensed to OnlineMedEd.

Figures 2.3a, 2.3b: Courtesy of WebPathology.

Figure 2.3c: Courtesy of Radiopaedia.